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CAMPYLOBACTER BACTEREMIA: A RARE AND UNDER-REPORTED EVENT?

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Bacteria belonging to the species *Campylobacter* are the most common cause of bacterial diarrhoea in humans. The clinical phenotype associated with *Campylobacter* infections ranges from asymptomatic conditions to severe colitis and bacteremia. In susceptible patients, *Campylobacter* infections are associated with significant morbidity and mortality, with both host factors and bacterial factors being involved in the pathogenesis of bacteremia. In the host, age, gender and immune-compromising conditions may predispose for *Campylobacter* infections, whilst the most important bacterial determinants mentioned in the literature are cytotoxin production and flagellar motility. The role of sialylated lipo-oligosaccharide (LOS) and serum resistance in bacteremia is inconclusive at this time, and the clinical significance of *Campylobacter* bacteremia is not yet fully understood. More emphasis on the detection of *Campylobacter* species from blood cultures in susceptible patients at risk for *Campylobacter* infections will increase our understanding of the pathogenesis and the relevance of *Campylobacter* bacteremia.

Keywords: *Campylobacter,* under-reported, bacteremia, complications, serum resistance

Historical background

The recognition of *Campylobacter* as a pathogenic bacterial species began in the early twentieth century, when in 1913 McFadyean linked the presence of *Vibrio*-like bacteria to previously unexplained abortions in cattle [1]. Smith confirmed this association in 1918 by isolating *Vibrio*-like bacteria from aborted bovine foetuses [2], eventually leading to the bacterium being designated *Vibrio fetus* in 1919 [3]. In 1931, Jones and Little reported that *Vibrios* were often cultured from inflamed small bowel mucosa during autopsies of cattle that had experienced diarrhoeal stools mixed with blood and mucus [4]. Further, the authors were able to reproduce this disease, based on Koch's guidelines, by feeding healthy animals pure cultures of micro-aerophilic-grown *V. fetus* bacteria, establishing that this bacterial species was indeed pathogenic [4].

In 1946, Levy reported that a microscopically observed *Vibrio*-like organism was the cause of a large outbreak of human gastroenteritis in Illinois, USA [5]. Remarkably, 19 of these 39 patients also harboured *Vibrio*-like organisms in their blood, establishing that these *Vibrio*-like organisms were indeed the cause of this large outbreak of gastroenteritis [5]. The study by Levy et al. provided strong evidence that the *Vibrio*-like organisms could enter the general circulation of affected individuals. Ten years later, King et al. reported that *Vibrios* obtained from various sources could be divided into two distinct groups: one group of *Vibrios* with the culture characteristics of the earlier described *V. fetus*; and a second a group of *Vibrios* commonly present in human blood. This second group comprised a bacterial subspecies that possessed a higher optimum growth temperature than the previously reported *V. fetus* [6]. King named this second group the *V. fetus*-related organisms, though these organisms were later re-designated as *Campylobacter fetus* ssp. *jejuni* by Smibert [7], and finally as *Campylobacter jejuni* (*C. jejuni*) by Véron and Chatelain [8] and Jones et al. [9]. More importantly, during the whole time period from 1930 to 1970, the *C. jejuni* bacterium was frequently reported to be associated with diarrhoeal stools (containing mucus and blood) and coincident blood infection [5, 10–12]. However, microbiologists failed to appreciate the significance of these findings during that time.

In 1971, Cooper and Slee noticed that a *Campylobacter* strain isolated from blood of a bacteremic patient was resistant to the antibiotic cephalotin, thereby establishing one of the first tools for routine *Campylobacter* detection using selective culture plates and growth (micro-aerophilic) conditions [13]. Dekeyser et al. described in 1972 a method enabling the separation of *Campylobacter* from normal flora

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by filtering stool suspensions through a 0.65-p.m membrane filter [14]. One year later, Butzler et al. made an important step forward in *Campylobacter* research showing that patients with diarrhoea were significantly more often culture-positive for *C. jejuni* and *Campylobacter coli* (*C. coli*) [15], using the technique of Cooper and Slee [13]. In 1977, Skirrow developed a protocol for *Campylobacter* culture media that finally avoided the use of a filtration step, allowing *C. jejuni* and *C. coli* to be cultured directly from stool samples on blood agar plates supplemented with antibiotics [16]. This technique allowed Skirrow to establish *C. jejuni* as a causative organism of diarrhoea, though the earlier observed link between gastroenteritis and the isolation of positive blood cultures with *Vibrio*-related (likely *C. jejuni*) bacteria, as suggested by Levy et al. and King et al., remained unappreciated in *Campylobacter* research.

Nowadays, *Campylobacter*, in particularly *C. jejuni*, has been established as the most common cause of bacterial gastroenteritis worldwide [17], with an estimated prevalence of 2–20 million cases annually in the 27 member states of the European Union alone [18, 19]. *Campylobacter* spp. may be isolated from a wide variety of animal and environmental sources, including cattle [20], dogs [21], ducks [22], goats [23, 24], monkeys [25], sheep [26, 27], shellfish [28] and contaminated water [29]. However, the most important source for human-related *Campylobacter* infections is chickens and the consumption of (undercooked) chicken meat [30].

A variety of post-infectious complications, including reactive arthritis (RA), Guillain–Barré syndrome (GBS) and Miller Fisher syndrome (MFS), have been associated with *Campylobacter* infections [31–35], with the latter two syndromes being linked to the expression of ganglioside mimics on the lipo-oligosaccharide (LOS) structures of certain *C. jejuni* strains. Essentially, upon infection, certain bacterial ganglioside mimics may facilitate the development of auto-antibodies to ganglioside structures present on the neurons of the host, leading to a temporary infection-associated paralysis [33]. Approximately 50–60% of *C. jejuni* isolates are able to express such sialic acid-containing ganglioside mimic sugar structures on their cell envelope [36], structures that have also been reported to promote intestinal epithelial cell invasion [37–39], human serum resistance [40, 41] and the ability to induce severe colitis in humans and monkeys [32, 42].

Recently, a much discussed issue has been the role of translocation in facilitating the spread of viable bacteria into the blood circulation, leading to a *Campylobacter*-related bacteremia [43–46]. Processes involving the translocation of *Campylobacter* through the intestinal mucosa may be the priming factor for the more serious disease complications associated with bacteremia.

Campylobacter-related bacteremia in humans

The first major steps in scientifically linking *C. jejuni* gastrointestinal infection to human bacteremia were taken in the 1980s, though isolation of the *Campylobacter* bacterium itself was still problematic. For example, in 1979, a 26-year-old man was hospitalized with acute colitis and associated bacteremia, and *C. fetus* spp. *jejuni* was isolated from the patient [44]. However, in a report published 2 years later, eight human neonates between the age of 2 and 11 days old were found to develop a *C. fetus* spp. *jejuni*-induced colitis, with the authors stating that bacteremia was not detected (neonatal sepsis being often associated with the acquisition of a pathogenic microorganism from the mother) [47, 48]. One of the major reasons for the contrast between these two reports may have been the relatively large number of *C. jejuni* bacteria required at that time to actually detect *C. jejuni* infection [49]. In fact, this problem could not be overcome until suitable selective culture media became available several years later.

In 1982, a German case study presented a 15-month-old boy who was hospitalized with high fever and symptoms of gastroenteritis, and *C. jejuni* was cultured from stool and blood using a special, innovative method [50]. Importantly, using this method it was concluded that *C. jejuni* bacteremia might occur more often in humans than was generally thought at the time, a conclusion matching the earlier unappreciated observations by King, who found that blood cultures were nearly always positive for *Vibrio*-related organisms (likely *C. jejuni* bacteria) in patients suffering from gastroenteritis (despite the limitations on *C. jejuni* detection at that time) [10]. However, it would take further research to reveal the exact association between *Campylobacter* gastrointestinal infection and bacteremia.

Surveillance of *Campylobacter* gastroenteritis and bacteremia

An increase in awareness of the international role of *Campylobacter* in facilitating gastrointestinal infections and bacteremia also occurred in the 1980s. For example, in September 1980 in Los Angeles, USA, there was a large outbreak of *C. jejuni*-related bacteremia. In this outbreak, 11 previously healthy individuals were hospitalized with acute febrile illnesses with blood cultures found to be positive for *C. jejuni*. No direct evidence was obtained that helped to reveal the source of this outbreak, although contaminated turkey consumption was suspected [51].

An 11-year surveillance study of laboratory reports sent to the Public Health Laboratory Service (PHLS) and Communicable Disease Surveillance Centre (CDSC) during the period 1981–1991 in England also reported on bacteremia. It was found that of 267,565 faecal samples, 394 were associated with episodes of *Campylobacter*-related bacteremia (of which 7 died from complications related to their *Campylobacter* infection) [52]. It was concluded from this study that a *Campylobacter*-related bacteremia occurs on average in 1.5 per 1000 diarrhoea cases, with *C. jejuni* and *C. coli* accounting for 89% of *Campylobacter*-related bacteremias. Further, age-related differences were observed, as the incidence of *C. jejuni* bacteremia in children between 1

and 4 years of age was reported as 0.3:1000 cases, whereas in patients >65 years of age the incidence of *Campylobacter*-related bacteremia increased to 5.6:1000 cases. Additionally, as many as 28% of the bacteremic patients suffered from underlying disease, with *C. jejuni* isolates of HS (heat stable) serotypes 4, 13, 16 and 50 being more frequently isolated from blood cultures. Importantly, 71% of the bacteremic patients experienced *Campylobacter*-related diarrhoea or other gastrointestinal problems, such as abdominal pain without diarrhoea or inflammatory bowel disease, indicating that *C. jejuni*-related bacteremia most likely developed during an acute attack of *Campylobacter* gastroenteritis. The conclusion of this 11-year surveillance study was that *Campylobacter*-related bacteremia was a transient complication of *Campylobacter* enteritis due to *C. jejuni* or *C. coli* in otherwise healthy individuals.

A later survey of *Campylobacter*-related bacteremia in three Danish counties over a period of 5 years (1989–1994) revealed that *C. jejuni* and *C. coli* were the most prevalent *Campylobacter* species associated with bacteremia in Denmark, and concluded that *Campylobacter*-related bacteremia was more common than previously thought [53]. Similarly, an 8-year prospective study in Spain on *Campylobacter*-related bacteremia (1987–1994) demonstrated that 26 of 30 bacteremia cases were caused by *C. jejuni*, with men being more susceptible to *C. jejuni* bacteremia than women [54]. In this study, 90% of the 30 bacteremic patients had immune-related problems, caused by underlying diseases or immuno-depressive or -suppressive therapies [54]. Perhaps not surprisingly, the mortality rate in these immunocompromised patients suffering from *C. jejuni*-induced bacteremia was high (30.8%), and death was found to be directly related to the bacteremia in 11.5% of the patients.

In contrast, a later nationwide study on *C. jejuni*- and *C. coli*-induced bacteremia in Finland indicated the opposite findings, claiming that relatively young individuals without underlying disease were mainly affected, with most isolates being susceptible to antimicrobials and favourable disease outcomes [55]. Other studies from Finland and Denmark estimated the annual incidence of *Campylobacter*-related bacteremia to be 0.2–0.29/100,000 [53, 56]. In these studies, it was estimated that for every 1000 gastroenteritis cases, three episodes of bacteremia could be detected, though this frequency may differ in hospital-based populations.

In a 5-year study involving 23 hospitals in the Paris area (2000–2004), 183 *Campylobacter*-related bacteremia cases were diagnosed, of which 5 patients recurrently developed bacteremia, and a total of 27 patients (15%) died within 1 month after the first culture-positive blood sample had been obtained [57]. In this French study, *C. fetus* was the most commonly identified species (53%) followed by *C. jejuni* (30%), and most cases involved male (70%), elderly (23%) and immunocompromised patients (81%) [57]. However, in Finland there were only four cases of *C. fetus*-related bacteremia reported in a 10-year surveillance study [55], suggesting that there may be geographical differences in *C. fetus*-related bacteremia. In fact, in the majority of clinical studies, *C. jejuni* and *C. coli* have been the predominant *Campylobacter* species isolated from *Campylobacter*-related bacteremia, and the risk of death has been higher in those patients that did not receive appropriate antibiotic therapy, or were prescribed a third-generation cephalosporin [58–62].

One possible reason for the different conclusions obtained in *Campylobacter*-related bacteremia studies may be the clinical setting in which the results are obtained. For example, in a hospital-based study, Tee and Wijch reported a prevalence of 1.6% for bacteremia in persons infected with *Campylobacter* [60]. However, in background population-based studies, *Campylobacter* bacteremia was observed to be 5–10 times less abundant, with reported mortalities being between 2 and 13% [56]. Further, the clinical setting may also be responsible for the differences reported between *C. jejuni*-induced bacteremia and patient age. In 1990, hospitalized children in the age group of 0–9 years were found to be most at risk for *Campylobacter*-related bacteremia, whereas in 2007, a population-based study indicated that elderly persons older than 60 years were more at risk [56].

Fernandez-Cruz et al. reported in a recent overview of *Campylobacter* bacteremia that only 0.24% of all hospitalized patients with blood stream infections could be associated with *Campylobacter* spp. and that these bacteremias were community-acquired in 81% of cases [62]. *C. jejuni* was the most often isolated bacterium next to *C. fetus* and *C. coli*. An overview of *Campylobacter*-related bacteremia, underlying disease and related complications is provided in *Table 1*.

In summary, the 1900–1970 literature shows that *Campylobacter* spp. were nearly always isolated from blood samples of gastroenteritis patients suffering from a *Campylobacter* infection. However, the development of new culture isolation protocols between 1970 and 1980 resulted in a shift from *Campylobacter*-based detection in patient blood cultures to detection on culture plates containing specific antibiotics. This meant that the detection of *Campylobacter* species became primarily associated with stool samples. Since that time, only a small percentage of gastroenteritis patients that are actually hospitalized due to bacteremia have been reported to be blood-culture-positive for the presence of *Campylobacter* bacteria, although the actual frequency of *Campylobacter*-related bacteremia is still under discussion. In this respect, the authors feel that *Campylobacter* is an under-reported cause of bacteremia, largely related to current hospital microbial culture techniques and the timing of detection in *Bacteremia* patients.

The detection of *Campylobacter*-related bacteremia

Blood culture

Though automatic blood culture systems tend to be routinely used in the majority of diagnostic microbiology

laboratories, relatively little information is available with respect to the performance of blood culture systems for the detection of *Campylobacter* species. The absence of specific *Campylobacter* isolation protocols, and the unknown sensitivity of these automated systems for the detection of *Campylobacter* spp., may be resulting in an underestimation of *Campylobacter*-related bacteremia. For example, a study on *Campylobacter pylori,* a taxonomically closely related species to *C. jejuni*, showed that this bacterium failed to grow in diagnostic blood culture systems [63]; the authors could find only a single study reporting a comparison of the performance of automated blood culture systems for the isolation of *Campylobacter* spp. from blood specimens. In that study, BACTEC 6B aerobic and 7D anaerobic bottles performed poorly in detecting *C. fetus* and *C. jejuni*, with the median growth rate in these diagnostic culture bottles being 5–10 days for *C. jejuni* and 3–5 days for *C. fetus* [49]. In contrast, the Roche Septi-Chek system appeared to perform much better, as it allowed a more rapid detection of *C. jejuni,* with the median incubation time reduced to 2–3 days [49].

However, no other study has been published on this subject to date. Importantly, in modern clinical microbiology laboratories, the incubation period for blood culture bottles is usually limited to 4–5 days. As the detection of *Campylobacter*-related bacteremia requires a median growth rate exceeding 5 days for a substantial proportion of isolates, it is therefore conceivable that many episodes of *Campylobacter*-related bacteremia go unnoticed. It has therefore been recommended by some authors that the contents of blood culture bottles should be sub-cultured onto solid media at the end of the standard 5-day incubation period [personal communication].

In addition, others have also mentioned that minimizing the time delay between the onset of fever and chills and the collection of blood culture samples may increase the detection rate of *Campylobacter* spp. from blood cultures, as the time delay between specimen collection and the actual processing of the specimen in the laboratory may further compromise the sensitivity of blood culture systems [64].

Molecular diagnostics

Molecular diagnostics tests are becoming widely used in many diagnostic microbiology laboratories, and techniques involving multiplex polymerase chain reaction (PCR) have already been developed to detect *Campylobacter* spp. in patient's stools [65, 66]. Further, these techniques can be used to detect culture-negative *Campylobacter* infections. For example, Morris et al. used molecular techniques (PCR) to detect *C. jejuni* in a culture-negative blood culture from a patient suffering from malaria [67]. Though not currently routinely used for the detection of *Campylobacter* spp., molecular testing is sure to make a large impact on the detection of *Campylobacter* infections in the future, including in the surveillance and treatment of *C. jejuni*-induced bacteremias.

Timing of detection in hospitals

Clinically, in industrialized countries, infection with *Campylobacter* commonly results in the development of diarrhoea with fever, though in most cases this disease is self-limiting and thought to occur without bacteremia [68, 69]. Remarkably, patients without bacteremia do get hospitalized with *Campylobacter*-related complications due to the reported presence of these bacteria in cerebrospinal fluid [40], liver [70, 71], thyroid gland [72], joints [73], bursitis [74], brain [75], axillary nerve [76], bone [77] and even heart [78, 79]. The detection of *Campylobacter* in these parts of the human body strongly suggests that *Campylobacter* species are able to travel through the patient's circulatory system without causing actual serious bacteremia that requires hospitalization, at least in the first days of infection.

Such complications have also been reported in patients hospitalized with *Campylobacter*-related bacteremia and underlying health problems such as *Campylobacter*-related meningitis [80, 81], hepatitis [82], arthritis [83], abdominal septic aortic pseudoaneurysm [84], peritonitis [85, 86], acute pancreatitis [87, 88], cellulitis [89, 90], pericarditis [91], endocarditis [92] and hemolytic uremic syndrome (HUS) [93]. Again, these reports indicate that *Campylobacter* is able to efficiently travel through the blood stream in gastroenteritis patients, specifically to tissues or organs that can only be reached via the circulating blood stream.

Campylobacter bacteremia in animals

Experiments in animal models demonstrated that *Campylobacter*-related bacteremia is very common in the early hours and days of a *Campylobacter*-induced infection. For example, Fitzgeorge et al. used a *C. jejuni* strain isolated from a gastroenteritis patient in a study involving rhesus monkeys, showing that these monkeys develop a mild disease after oral inoculation but, remarkably, remain secreting *C. jejuni* in their faeces for a prolonged period [94]. Culture of *C. jejuni*-infected monkeys revealed that this bacterium was mainly found in the intestinal tract, and also in the liver and gall bladder, even after 30 days of infection [94]. Interestingly, four out of the six monkeys tested also developed a bacteremia within the first 3 days of infection, indicating that *C. jejuni* is able to pass the gastrointestinal epithelial barrier of rhesus monkeys very quickly after oral administration [94], an observation that may also be true in humans [64].

C. jejuni infection of outbred HA-ICR adult mice (a mouse developed by Hauschka (HA) at the institute for cancer research (ICR)) resulted in bacteremia within the first hour of infection [95]. Moreover, in that study mice were still colonized 14 months after infection and remained secreting *C. jejuni* in their stool [95]. These HA-ICR mice were not ill, none died and the main colonization sites were the stomach and the small intestines.

Exposure of rabbits to *C. jejuni* in a "removable intestinal tie adult rabbit diarrhoea" (RITARD) model resulted in enteritis, with loose and mucus-containing stools. Further, 27 of the 30 rabbits (96%) in this study suffered from bacteremia within the first 24 h of infection, a frequency that declined to 26% after 96 h [96]. These results indicate that *C. jejuni* may efficiently translocate into the blood stream in a RITARD model of infection. However, although the authors claimed that the RITARD model was a good model for *C. jejuni*-induced human disease, more than half of the rabbits died, which is unusually high when compared to *C. jejuni*-induced illness in humans.

In a separate animal model, neonatal calves infected with *C. jejuni* only sporadically developed bacteremia, with the bacterium being mainly cultured from the ileum, caecum, colon and bloodstream after 1–3 weeks infection [97].

Rodent and small animal models tend to give different results with respect to *Campylobacter* species and the development of bacteremia. For example, human clinical *C. jejuni* isolates display low virulence and no bacteremia in guinea pigs, whereas *C. fetus* tends to be more aggressive and better able to induce bacteremia in these animals [98]. Infection experiments with ferrets, after feeding or by gavage challenge, revealed that 38 out of 40 animals became colonized by *C. jejuni*, and that the subsequent diarrhoea lasted 2–4 days, with at least 20% of the animals developing bacteremia 2–5 days after inoculation [99].

Taken together, these animal model experiments show that gastrointestinal infection and colonization with *Campylobacter* spp. (and with *C. jejuni* in particular) is indeed associated with subsequent *Campylobacter*-related bacteremia in the first hours and days of infection, often leading to the further dissemination of this bacterium to different organs of the body, for example, mainly to the lymphoid-related tissues, spleen and liver in chickens [100, 101].

C. jejuni virulence factors associated with bacteremia

In view of the importance of *C. jejuni* in human disease, there is still relatively little known about the virulence mechanisms utilized by this pathogen.

Cytotoxin

In 1983, a cytotoxin was discovered in *C. jejuni* that was mainly associated with isolates that induced acute gastroenteritis and/or bacteremia [102]. Further, a cytopathic effect was observed when Hela cells were treated with filtrates from 48-h *C. jejuni* cultures. This effect could not be reproduced when the filtrates were heated or treated with trypsin, indicating that the cytotoxin was most probably a protein [102]. Further, in a RITARD model of infection, rabbits developed bacteremia and severe watery mucus-containing diarrhoea (some even died) when exposed to *C. jejuni* cytotoxin-positive strains, whereas rabbits inoculated with cytotoxin-negative *C. jejuni* isolates developed less severe diarrhoea and none died [103]. Other toxins have been described for *Campylobacter* spp., such as enterotoxin, Shiga-like toxin, hemolytic cytotoxins, hepatotoxin and the until now best characterized cytolethal distending toxin [104]. Whether some of these toxins are involved in *Campylobacter*-related bacteremia remains to be elucidated. Overall, the cytotoxin study from 1983 defined one of the first *C. jejuni* virulence factors associated with *Campylobacter*-related bacteremia.

Flagella

In a Japanese study, a motility-impaired flagella knockout mutant of *C. jejuni* was unable to induce bacteremia in mice as compared to its isogenic wild-type strain [105]. In fact, the importance of the flagella in *Campylobacter* virulence has been highlighted in many studies, including those using both *in vivo* animal models and *in vitro* models based on cell culture systems [106–108]. Further, Konkel et al. clearly demonstrated that functional flagella are required for the secretion of important *Campylobacter* virulence factors that are required to establish a maximal invasion of INT 407 intestinal epithelial cells. With particular respect to *Campylobacter*-related bacteremia, it is hypothesized that the *Campylobacter* flagella provides motility, enabling the bacterium to traverse through the gastrointestinal mucus layer and reach the epithelium of the intestine ready for translocation into the blood stream [107].

Virulence-associated genes

In a previous publication, the current authors analyzed whether there was a link between the frequency of occurrence of the virulence-associated genes *Cj*0486, *cadF, ciaB*, *iamA*, *virB8*, *virB9* and *virB11* [109]. A link was found between isolates possessing a low capacity to invade cells and the absence of *Cj0486* and *ciaB* [109]. A later independent study did not find any link between the virulence genes *iamA, cdtB, virB* and *capA* and invasiveness (blood isolates) or enteric (faecal isolates) infection in Denmark [110]. Further research in this area would be very useful in helping to identify bacteremia-related virulence factors.

HS serotype and lipo-oligosaccharide (LOS)

In a large South African study between September 1982 and August 1983, 258 clinical *C. jejuni* ($n = 250$) and *C. coli* ($n = 8$) strains were isolated from children with symptoms of gastroenteritis and/or bacteremia [111]. Although it was not clear how many isolates were obtained from bacteremic patients, serotyping of the different isolates did reveal that *C. jejuni* isolates with HS serotypes 2, 4, 11, 19 and 33 were more frequently associated with bloody

stools or mucus secretion during the diarrhoeal episode [111]. From this data, it was concluded that HS serotypes 2, 4, 12, 19 and 33 could potentially harbour a common bacterial virulence factor that is involved in triggering a more severe gastroenteritis phenotype. In a later study using the RITARD rabbit model, it was observed that *C. jejuni* strains possessing different HS serotypes varied in their ability to colonize the intestine of rabbits to cause bacteremia and to stimulate primary intestinal and serum antibody responses [112], suggesting that a bacterial component is involved in the induction of *C. jejuni*-induced bacteremia. Research into this interesting observation is still continuing, with more recent evidence suggesting a mechanism by which the HS serotype could be involved in *Campylobacter*-related bacteremia. For example, a recent study by Mortensen et al. in Denmark revealed that severe gastroenteritis and bloody stools were associated with the expression of ganglioside epitopes present on LOS [32], and a recent analysis of a Dutch library of *C. jejuni* isolates revealed that the expression of such ganglioside-like epitopes is also particularly associated with LOS HS serotypes 2, 4, 11, 19 and 33 (Heikema et al., manuscript in preparation). These observations provide evidence for a possible link between HS serotype and the bacteremic potential of *C. jejuni*. Certainly, ganglioside-like epitopes have been linked to the ability of *C. jejuni* bacteria to invade intestinal epithelial cells when compared to isolates lacking such structures [38], though whether this phenomenon actually contributes to an increased risk of bacteremia remains to be determined.

Serum resistance and the immune response

The potential involvement of the capsule and sialylated LOS in serum resistance has been corroborated in a study by Field et al., who showed that virulent *C. jejuni* isolates are better protected against serum and that both capsule and sialylated LOS appear to contribute to increased virulence [37–39, 113]. Further, a recent study by Keo et al. established that capsule expression was essential for *Campylobacter* resistance to human serum [114], though, in contrast to earlier reports [41, 115], they did not find any essential contribution of sialylated LOS to serum resistance [114]. Therefore, the actual involvement of LOS in serum resistance is still under discussion.

C. fetus also exhibits resistance to human serum, via expression of surface (S-) layer structures that disable the binding of complement component C3b, such that isolates lacking surface (S-) layer structures are found to be sensitive to human serum [116].

With respect to the immune response, a *C. fetus* infection in an immunocompromised individual was reported to lead to a relapse in infection after 7 years, the relapse being attributed to the absence of specific *C. fetus*-directed antibodies. This study indicated that a functional immune system is essential for protection against *C. fetus*-related blood infections [117]. Unfortunately, at present no literature is available on this interesting subject with respect to *C. coli* infections.

To assess the contribution of immune cells to *Campylobacter* disease, Wassenaar et al. studied the ability of macrophages and monocytes to phagocytose and kill *C. jejuni* bacteria [118]. They showed that most healthy donors possessed macrophages and monocytes that could efficiently kill particular *C. jejuni* isolates within 24–48 h after bacterial exposure, though 10% of donors harbored macrophages and monocytes that were incapable of actually killing the phagocytosed *C. jejuni* bacteria [118]. The main conclusion of this study was that individuals carrying macrophages that are unable to destroy phagocytosed bacteria probably have an elevated risk of developing bacteremia and other complications during a *Campylobacter* infection [118].

An interesting phenomenon has been observed in long-term poultry workers who are continuously exposed to *C. jejuni* and other *Campylobacter* spp. bacteria. This continued exposure apparently leads to a specific IgG antibody response, which is mainly targeted against the bacterial flagella and an uncharacterized 40-kDa protein, possibly providing effective protection against *Campylobacter*-induced disease. This suggests that the *Campylobacter* flagellum and the 40-kDa protein are potential interesting targets for vaccine development [119].

Conclusion

The studies discussed in this systematic review illustrate that *Campylobacter*-related species may be an under-reported event facilitating organ and tissue infections in both animals and humans.

From a human perspective, host risk factors for *Campylobacter*-related bacteremia include age (being a neonate <1 year, adult between 15 and 44 years of age and elderly >65 years), gender (being male), and most importantly the host's immune status prior to bacterial exposure. Bacterial risk factors associated include the expression of a cytotoxin, the presence of flagella and serum resistance. Additionally, specific HS serotypes may also play a role in increasing the risk of bacteremia.

Many of the past and present cases of *Campylobacter*-related bacteremia are likely to go unnoticed, as *Campylobacter* infections are often self-limiting in healthy people. Moreover, the conventional *Campylobacter* detection techniques currently utilized within diagnostic microbiology laboratories may not be optimal for the efficient detection of *Campylobacter*-related bacteremia, and the introduction of more sensitive molecular detection techniques may be beneficial in this respect.

Finally, our lack of knowledge regarding *Campylobacter* infection and subsequent bacteremia contrasts greatly with our current knowledge regarding *Campylobacter* infection and the development of GBS. Therefore, increased efforts should be made to provide more accurate data on the prevalence and mechanisms that facilitate *Campylobacter*-related bacteremia.

Table 1. *Campylobacter*-related bacteremia, patient status and bacteremia-related complications

Species*	No. of patients†	Underlying diseases‡	Bacteremia-related complication§	Year**	Ref.††
C. fetus spp. *jejuni*	1	None	None	1979	[44]
C. jejuni/coli	5	None	None	1977–1979	[64]
C. jejuni	11	None	None	1980	[51]
C. fetus spp. *jejuni*	8	None	None	1981	[48]
C. jejuni/coli/fetus	394	28% of all cases	10 patients	1981–1991	[52]
C. jejuni	6	None	Death in two patients	1992	[120]
C. jejuni	2	HIV	None	1992	[121]
C. jejuni	28	HIV	None	1991–1993	[122]
C. jejuni	1	Chronic GVHD	GBS	1994	[123]
C. jejuni/coli	7	Immune-deficient	None	1994	[124]
C. jejuni/coli/fetus	14	Immunological, neoplastic and vascular diseases	Cutaneous cellulitis or vasculitis and 1 death	1989–1994	[53]
C. jejuni	1	Acute lymphoblastic leukaemia	None	1995	[125]
C. jejuni	2	HIV	None	1995	[126]
C. jejuni	1	Immunocompromised	None	1997	[127]
C. jejuni	1	Renal patient	GBS	1998	[128]
C. jejuni	21	HIV	Cellulitis 1 patient	1998	[60]
C. jejuni	2	AIDS	Death	1999	[129]
C. jejuni/coli	76	70% none underlying diseases	2 deaths, 1 GBS, 1 spondylodiscitis	1998–2007	[55]
C. jejuni/fetus	2	Splenectomy for hypersplenism	None	1999	[130]
C. jejuni	1	CAPD	Peritonitis and chronic pancreatitis	2000	[85]
C. jejuni	1	Autoimmune haemolytic anaemia	None	2001	[131]
C. jejuni	1	X-linked agammaglobulinemia	Pericarditis	2002	[91]
C. fetus	2	None	Cellulitis and septic arthritis	2003	[89]
C. jejuni	1	Immunocompromised	Cellulitis	2004	[90]
C. fetus	1	None	None	2005	[132]
C. jejuni	2	Immuno-suppressive concomitant diseases	Hemathemesis	2006	[133]
C. fetus	1	Urinary tract infection by *E. coli* and immune suppressed	None	2006	[134]
C. fetus/ *Campylobacter* spp.	183	Immunocompromised, liver disease, cancer	27 patients died	2008	[135]

Table 1. *Continued*

Species*	No. of patients†	Underlying diseases‡	Bacteremia-related complication§	Year**	Ref.††
C. jejuni	1	None	Septic aortic pseudoaneurysm	2009	[84]
C. jejuni	1	CAPD	None	2009	[136]
C. jejuni	2	Renal patient	None	2010	[137]
C. jejuni	1	X-linked agamma-globulinemia	None	2010	[138]
C. jejuni/fetus	2	Alcoholism	None	2011	[139]

*The different *Campylobacter* species isolated from these bacteremia patients.
†The number of patients analyzed.
‡The underlying disease which some of the patients were experiencing before the induction of bacteremia.
§Complications that were induced during a *Campylobacter* bacteremia.
**Year of the shown study.
††Reference number of the article from which the information was retrieved.
A selection of *Campylobacter*-related bacteremia patients are shown, hospitalized between the years 1979 and 2011.

Search strategies and selection criteria

Relevant scientific articles were identified via targeted searches of PubMed, Embase, MeSH and Cochrane databases for articles published before 20 December 2011. The terms "*Campylobacter jejuni*" and "bacteremia" or "*Campylobacter fetus*" and "bacteremia" or "*Campylobacter*" and "bacteremia" were used as search terms. Analysis was not restricted to only English or American language articles. These broad search terms were chosen in order to generate the most complete set of references for the topic being presented in this review.

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